INTERNAL MEDICINE JOURNAL

Assessing understanding of individual risk and symptoms of progressive multifocal leukoencephalopathy in patients prescribed natalizumab for multiple sclerosis

Louise Rath, Nirosen Vijiaratnam† and Olga Skibina

Neurology Department, Alfred Health, Melbourne, Victoria, Australia

Key words
multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy, early detection, patient education, patient engagement.

Correspondence
Louise Rath, Neurology Department, Alfred Health, Commercial Road Melbourne, Vic. 3004, Australia.
Email: l.rath@alfred.org.au

Received 2 August 2016; accepted 9 October 2016.

doi:10.1111/imj.13318

Abstract

Background: Natalizumab, a monoclonal antibody directed against α4 integrin, is a highly efficacious treatment commonly used in relapsing remitting multiple sclerosis. Natalizumab is associated with the potentially fatal, rare, demyelinating, opportunistic brain infection, progressive multifocal leukoencephalopathy (PML). Prognosis and disability from PML are determined by early diagnosis.
Aims: Written tools are mandated in Australia and other prescribing countries with the aim to help patients understand the risks associated with treatment and ensure familiarity with the early symptoms of PML. We aimed to assess if these tools achieve such an outcome.
Methods: A cross-sectional survey was conducted using a convenience sample of multiple sclerosis patients prescribed natalizumab presenting to the infusion centre at a major tertiary hospital. Patients were offered a multi-choice questionnaire to assess their knowledge on the treatment risks and surveillance requirements of their therapy. Three specific questions were highlighted by the researchers as crucial to patient understanding of PML and defined as basic knowledge.
Results: A total of 48 patients in our hospital was prescribed natalizumab; 37 responded. A total of 16 (43.2%) patients answered all three basic knowledge questions correctly. There was no difference in the ability to answer these questions based on length of treatment or co-ownership knowledge between patients with base knowledge and without.
Conclusion: Natalizumab is associated with an increased risk of PML. Early detection and treatment of PML results in improved patient outcomes. Patient knowledge and co-partnership in the utilisation of PML risk tools is relevant in ensuring early detection. Our findings question the ability of currently sanctioned tools to inform patients of basic knowledge of PML and their risk of developing PML. A future study with a repetitive education approach and repeating the questionnaire at multiple time points would be of interest.

Introduction

Natalizumab, a monoclonal antibody directed against α4 integrin, is a widely used, highly effective monotherapy in the treatment of relapsing remitting multiple sclerosis (MS). Natalizumab is associated with a potentially fatal, but rare, demyelinating opportunistic brain infection, progressive multifocal leukoencephalopathy (PML). The development of PML during natalizumab treatment is linked to the presence of antibodies against the John Cunningham Virus (JCV), length of natalizumab treatment and prior immunosuppression.[1–4]

There have been 664 confirmed cases of natalizumab-associated PML to date, with a global incidence of 4.22 per 1000 patients. The overall prognosis is poor, with a 23% mortality rate at 6 months, with surviving patients suffering from varying levels of

†Present address: Monash Medical Centre, Clayton Road, Clayton, Vic. 3168, Australia.
Funding: None.
Conflict of interest: L. Rath – travel grants from Biogen and Novatis and Speakers Honorarium from Biogen, Novartis and Genzyme; N. Vijiaratnam – unconditional educational grants from Ipsen and Biogen and travel grants from Ipsen and Abbvie; O. Skibina – research grant from Biogen, travel grants from Biogen, Novartis and Bayer and Speakers Honorarium from Bayer, Biogen, Genzyme and Novartis.

disability.[5] Although asymptomatic PML patients are more likely to survive and have better long-term function, the vast majority of patients diagnosed with PML have symptoms[5] that include progressive personality changes; speech, motor, retrochiasmal visual deficits; and new seizure onset.[6]

Prognosis is determined by a shorter time from first symptoms to confirmed diagnosis either clinically or by magnetic resonance imaging (MRI) surveillance. Early diagnosis, immediate cessation and removal of nataizumab results in better patient outcomes.[7–9]

Early detection of symptoms and compliance with surveillance tools by healthcare providers (HCP) is therefore vital. Vigilance through knowledge and engagement by patients and significant others is also crucial.

The Australian Therapeutic Goods Administration (TGA) mandates specific conditions of registration that aim to monitor and minimise the risk of PML. This requires HCP to perform online training prior to prescribing treatment with natalizumab and patients to give written informed consent.[5] The consent process outlines the association of natalizumab with PML, and patients must sign this in conjunction with receiving an alert wallet card and Consumer Medical Information (CMI) booklet. At each infusion, a signed questionnaire screening for symptoms of PML is also mandatory (Supporting Information Figs S1–S4).

We aimed to assess in a site compliant with TGA requirements, patients understanding of their individual risk of PML, knowledge of the potential symptoms of PML and their engagement in detecting possible symptoms of PML. Patients' knowledge of MRI surveillance and anti-JCV antibody surveillance time frames were also assessed.[8,9] Further analysis assessed if there was a difference in how patients who performed well on three basic PML knowledge questions, which were deemed critical, answered remaining questions when compared with patients who did not perform well.

Methods

This cross-sectional survey was conducted using a convenience sample of patients prescribed natalizumab presenting to the infusion centre at a major tertiary hospital. An accredited Health Research and Ethics committee at a major tertiary hospital approved this study.

Patient selection and survey administration including pilot

Patients with a diagnosis of MS currently prescribed natalizumab at one major tertiary hospital were offered an 18-question multi-choice survey to complete. Eligible patients were required to be over 18 years old and be able to read English. A window of 2 months for survey completion was allocated to attempt to capture all eligible patients.

During the survey period, there were 48 patients prescribed natalizumab at this hospital. A brief information sheet was given outlining the purpose, procedure and aims of the study. Formal cognitive assessment was not undertaken on all patients prior to the study; however, no concerns were raised about the cohort's cognition at time of survey completion, and they were deemed competent to sign consent based on the expanded disability scoring system functional score – mental. Patients were not selected on JCV antibody results or length of time on natalizumab, but available data indicated that 34 patients were JCV antibody-negative, and 14 patients were JCV antibody-positive.

Assessors were blinded to the patient's identity on questionnaire sheets.

Survey development

The survey was developed in consultation with a panel of MS nursing experts and a medical leader in Melbourne. After a review of available literature regarding natalizumab-associated, PML key themes emerged on the improved patient outcomes of asymptomatic and early symptomatic PML diagnosis. MRI surveillance and regular clinical review by clinicians have improved early detection, but the group felt that improved patient knowledge would promote another surveillance tool to detect early symptomatic PML and assist in compliance with MRI and clinic visits. This formed the basis for question development, patient knowledge and co-partnership of surveillance tools.

Pilot

The survey was piloted on four MS patients prescribed natalizumab at another major tertiary hospital. Clarity in language was addressed and order of questions revised. It was confirmed that the questionnaire could be completed in 10 min. Multi-choice questions were chosen with one correct answer.

Questions were divided into six key focus areas. Basic PML knowledge was assessed using three simple questions about patients being aware that PML is a brain infection, with common symptoms being cognitive and behavioural changes. A third question related to significant others' and families' awareness of common PML symptoms. This question addressed the

possibility of patients' lack of insight because of cognitive problems or symptoms being so subtle that HCP may not detect on examination.[8–10] Two questions focused on co-ownership of risk management by patients. This included knowledge of individual JCV antibody levels and frequency of testing as well as individual MRI scheduling for surveillance. Two questions looked at available approved resources (alert wallet card and pre-infusion questionnaire) and their utilisation by patients. Finally, we asked single questions on patients' request for involvement in decision making, factors influencing risk and number of years on infusion. All questions were multi-choices and had three or four options.

The results of multi-choice questions were assessed as correct or incorrect. For further analysis of results, the cohort was then divided into two subgroups based on one key focus area, correct PML basic knowledge (Basic) or incorrect PML basic knowledge (Nil-Basic). These two groups were then analysed against the remaining five key focus areas. Comparisons between groups were made using the Chi-squared test for equal proportions or Fisher's exact test for the key questions. Duration in years on natalizumab treatment was compared using the Mann–Whitney *U*-test with results reported as medians and ranges. A *P* value less than 0.05 indicated statistical significance.

Results

A total of 48 patients at the centre was prescribed natalizumab during the survey window. All patients complied with the TGA directive of written consent, receiving an alert card and CMI booklet prior to commencing natalizumab. Signed and completed pre-infusion questionnaires prior to each infusion were available in all medical records, with signed acknowledgement that they had read the CMI booklet in the last 24 h prior to infusion. Over three quarters of patients prescribed natalizumab completed the survey.

Basic demographics available for this cohort included gender ratio (male 33%, female 67%) (age 20–29 years 10%, 30–39 years 26%, 40–49 years 37%, 50–59 years 21% and over 60 years 6%). The age and gender distribution is typical for people living with MS.

Three of the questions on PML knowledge were ranked as the most significant by the researchers in promoting early detection of PML. These three questions were classified as PML basic knowledge. Analysis showed that 43.2% (16/37) of participates were able to answer all three PML basic knowledge questions correctly. In separating the three questions, 75.7% correctly knew that PML was a brain infection, 70.3% accurately knew the common symptoms of PML and 56.8% had informed their families or significant others of possible PML symptoms.

Co-ownership of risk management by patients revealed a 64.9% accuracy on the knowledge of frequency of JCV antibody testing, 51.3% knowledge of individual JCV index results and 43.2% on individual MRI surveillance time frames.

Compliance with the mandated alert wallet card demonstrated that 56.8% were no longer carrying this card, and 18.9% were not reading the pre-infusion questionnaire and reporting symptoms prior to their infusion but continuing to sign the form and proceed with the infusion. A total of 81.1% of the participants had knowledge of two of the key factors influencing PML risk, duration of time on prescribed natalizumab and JCV antibody index.

Further sub-analysis divided patients into basic knowledge PML correct (Basic), $n = 16$, and basic knowledge PML incorrect (Nil-Basic), $n = 21$, groups. These groups were then compared again with the focus areas (Table 1, results).

Discussion

To our knowledge, this is the first study that evaluates the understanding of basic PML knowledge of patients

Table 1 Results: comparison of Basic and Nil-Basic knowledge of PML groups

Questions	Basic ($n = 16$)	Nil-Basic ($n = 21$)	*P* value
Wallet alert card compliant	56.3%	33.3%	0.16
Pre-infusion questionnaire compliant	93.8 %	71.4%	0.11
Co-ownership of surveillance tests. JCV antibody screening and MRI	37.5 %	19.1%	0.27
Involvement desired in risk management due to satisfaction of knowledge	50 %	52.4%	0.89
Years on natalizumab treatment, median (range)	18 (2–48)	18 (3–66)	0.91
Knowledge of other factors affecting risk	93.8%	81 %	0.36
Cessation of natalizumab with PML	93.8%	57.1%	0.023

The results in *P* demonstrated that there was no significant difference between the two groups (Basic PML knowledge and Nil-Basic PML knowledge) for any of the focus areas. JCV, John Cunningham virus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy.

prescribed natalizumab. Studies on PML have primarily focused on clinical detection of symptoms and MRI detection plus supportive regimes during immune reconstitution and are aimed at improving HCP knowledge.[11,12] This study investigated whether TGA-mandated patient resources for natalizumab were sufficient in ensuring patients had a basic knowledge of PML. Possessing basic knowledge would ensure additional surveillance in conjunction with MRI, clinical and laboratory review in promoting early detection of PML. Our secondary aim was to determine if patients who possessed basic knowledge of PML were partners with their HCP in risk management procedures, were more likely to comply with mandated resources and, ultimately, be comfortable with their HCP decision making.

Our site is compliant in the discussion on PML risk before initiating therapy and also in the use of recommended TGA resources. Continual vigilance via MRI monitoring, clinical and laboratory review occurs as per local risk management protocol. Our results, however, indicate that standard tools are not sufficient in engaging patients in basic knowledge of PML and the education of the long-term relevance of these tools in facilitating early detection of PML by patients, families and significant others.

Active patient participation in individual healthcare is a key domain of safety.[13,14] Providing patients with information that encourages participation, such as communicating with health professionals, knowledge of individual surveillance regimens and key symptoms of concern in natalizumab-associated PML, all ensure safety and best outcomes for the individual.

Patient engagement and patient knowledge, however, is much more than 'signing off' on mandated or recommended tools. Previous studies have found written consent alone to be of limited value in engaging patients. Lack of recall and understanding shortly after the consenting process has been highlighted.[15] The TGA-mandated written consent prior to commencing natalizumab demonstrates similar findings in our study. Knowledge is a prerequisite of informed decision making, and consent alone, at one time point, does not engage individuals to seek or retain knowledge. This is especially relevant with natalizumab where cumulative risk caused by the increasing duration of treatment or conversion of JCV status supports our findings that repetitive education and knowledge assessment at regular time points is crucial.[16]

A similar survey on patient risk perception in mitoxantrone-treated patients also demonstrated that patient knowledge was insufficient.[17] Poor patient education retention has been highlighted in several other patient populations. This echoes the implications of our results that repetitive education and assessment at regular time points over treatment course should be encouraged and possibly mandated.[18–20]

The remaining TGA resources, CMI, wallet alert card and pre-infusion questionnaire also appear from our results not to fully engage patients in obtaining/retaining relevant knowledge. Patient engagement also relies heavily on an individual's health literacy. If people cannot process, understand basic health resources and act on them, they will be unable to determine the relevance of PML knowledge and risk of them.[21]

It is plausible to suggest from our results that Basic patients did engage better than Nil-Basic patients in safety tools, such as questionnaires prior to infusion (94–71%), because some knowledge has given them insight into the impact PML would have on them. Their basic knowledge also enabled them to understand the risk factors of contributing to PML as well as the importance of the early cessation of treatment.

Limitations

The study was limited to one MS-specific clinic in a major tertiary hospital and may not be reflective of other sites. Nonetheless, all other hospitals in Australia follow standard protocols driven by TGA guidelines and Biogen recommendations on the Tysabri Australasian Prescribing Program (TAPP) website. Similar risk management has been adopted in the United States with the mandated Tysabri Outreach: Unified Commitment to Health (TOUCH) programme.[22] We did not have the opportunity to discuss with patients their results and to ascertain further the reason for the lack of knowledge. We were also unable to explore the unexpected results of the lack of discussion on PML with family and friends because of anonymity. It is also unclear from our study if organisational factors are relevant, such as whether a delay in assessments after notification of symptoms using the pre-infusion questionnaire would deter patients from reporting.

The current mandated TGA resources that patients receive might have also contributed to our results. These written resources, whilst updated on current risk levels, have not been evaluated since approval and may not be providing information for patients that best meets their individual need or in a format that is meaningful to them. Australian data suggest that in patients over 40, factors such as education level and occupation influence the level of health literacy.[23,24] Frequency pictographs have been demonstrated to be easier for patients to identify with and comprehend. Unfortunately, the current available resources have not been adapted to this format. These influences may have affected our results as we have not included demographics and education into analysis. It may also be

that these resources are designed at a level of health literacy that not all our patients can interpret.

Conclusion

We found patients understanding of their treatment and its most critical risk to be poor. Our findings question the value of current mandated tools and the process of informed consent. This simple questionnaire may be of value in assessing patients' understanding of their treatment and individualising further education. A repeat evaluation of the success of this approach would be of interest and possibly benefit patients.

References

1 Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A *et al.* Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012; **366**: 1870–80.

2 Brew B, Davies N, Cinque P, Clifford DB, Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. *Nat Rev Neurol* 2010; **6**: 667–79.

3 Sorensen PS, Bertolotto A, Edan G, Giovannoni G, Gold R, Havrdova E *et al.* Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. *Mult Scler* 2012; **18**: 143–52.

4 McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, Molyneux P *et al.* Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. *J Neurol Neurosurg Psychiatry* 2016; **87**: 117–25.

5 Biogen Australia Pty Ltd. Tysabri Australasian Prescribing Program (TAPP). [cited 2016 Jul 28]. Available from URL: http://tapp.com.au/

6 Cordioli C, Rossi N, Rasia S, Lodoli G, Capra R. Early detection and favourable outcome of natalizumab-related progressive multifocal leukoencephalopathy (PML) in two multiple sclerosis patients. *Neurol Sci* 2015; **36**: 489–91.

7 Dong-Si T, Richman S, Wattjes M, Wenten M, Gheuens S, Phillip J *et al.* Outcome and survival of asymptomatic PML in natalizumab treated MS patients. *Ann Clin Transl Neurol* 2014; **1**: 755–64.

8 Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S *et al.* Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2014; **76**: 802–12.

9 Vermersch P, Kappos L, Gold R, Foley JF, Olsson T, Cadavid D *et al.* Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. *Neurology* 2011; **76**: 1697–704.

10 Hoepner R, Klotz P, Faissner S, Schneider R, Kinner M, Prehn C *et al.* Neuropsychological impairment in natalizumab-associated progressive multifocal leukoencephalopathy: implications for early diagnosis. *J Neurol Neurosurg Psychiatry* 2016; **87**: 224–6.

11 Kappos L, Bates D, Edan G, Eraksoy M, Garcia-Merino A, Grigoriadis N *et al.* Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol* 2011; **10**: 745–58.

12 Kappos L, Bates D, Hartung HP, Havrdova E, Miller D, Polman CH *et al.* Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol* 2007; **6**: 431–41.

13 Fagerlin A, Zikmund-Fisher B, Ube P. Helping patients decide: ten steps to better risk communication. *J Natl Cancer Inst* 2011; **103**: 1436–43.

14 Coulter A, Ellins J. Effectiveness of strategies for informing, educating, and involving patients. *BMJ* 2007; **335**: 24–7.

15 Turner P, Williams C. Informed consent: Patient listens and read, but what information do they retain? *N Z Med J* 2002; **115**: 1164.

16 Heesen C, Kasper J, Fischer K, Kopke S, Rahn A, Backhus I *et al.* Risk knowledge in relapsing multiple sclerosis (RIKNO 1.0) – development of an outcome instrument for educational interventions. *PLoS ONE* 2015; **10**: e0138364.

17 Hofmann A, Stellmann JP, Kasper J, Ufer F, Elias WG, Pauly I *et al*. Long-term treatment risks in multiple sclerosis: risk knowledge and risk perception in a large cohort of mitoxantrone-treated patients. *Mult Scler* 2013; **19**: 7920–5.

18 Williams A, Lindsell C, Rue L, Blomkains A. Emergency Department education improves patient knowledge of coronary artery disease risk factors but not the accuracy of their own risk perception. *Prev Med* 2007; **4**: 4520–5.

19 Chan Y, Nagurka R, Richardson LD, Zaets SB, Brimacombe MB, Levine SR. Effectiveness of stroke education in the emergency department waiting room. *J Stroke Cerebrovasc Dis* 2010; **19**: 209–15.

20 Lane D, Ponsford J, Shelley A, Sirpal A, Lip GY. Patient knowledge and perception of atrial fibrillation and anticoagulation therapy: effect of an interventional programme. The West Bermingham. Atrial Fibrillation Project. *Int J Cardiol* 2006; **110**: 354–8.

21 Siegel CA. Lost in translation: helping patients understand the risks of inflammatory bowel disease therapy. *Inflamm Bowel Dis* 2010; **16**: 2168–72.

22 Biogen Idec Pty Ltd. Touch, Tysabri Outreach: Unified Commitment to Health. [cited 2016 Mar 10]. Available from URL: http://www.touchprogram.com

23 Johnson A. Health literacy, does it make a difference? *Aust J Adv Nurs* 2014; **31**: 39–45.

24 Australian Commision on Safety and Quality in Health Care. *Health Literacy: Taking Action to Improve Safety and Quality*. Sydney: ACSQHC; 2014.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1. Therapeutic Goods Administration tools pre-infusion questionnaire. Biogen gives permission for the images and content of any of their Risk Management Plan (RMP) materials for the express purpose of use in a study/publication for medical research/investigations. © Biogen.
Figure S2. Therapeutic Goods Administration tools consent. Biogen gives permission for the images and content of any of their Risk Management Plan (RMP) materials for the express purpose of use in a study/publication for medical research/investigations. The material is © Biogen.
Figure S3. Therapeutic Goods Administration tools Consumer Medical Information. Biogen gives permission for the images and content of any of their Risk Management Plan (RMP) materials for the express purpose of use in a study/publication for medical research/investigations. © Biogen.
Figure S4. Tysabri Patient Alert Card. Biogen gives permission for the images and content of any of their Risk Management Plan (RMP) materials for the express purpose of use in a study/publication for medical research/investigations. © Biogen.

The not so innocent heart murmur: a 5-year experience

Shaw-Hua Kueh,[1] Thomas Pasley,[1] Miriam Wheeler[1] and James Pemberton[2]

[1]Department of Cardiology, Auckland Hospital, Auckland, and [2]Department of Cardiology, Dunedin Hospital, Dunedin, New Zealand

Key words
heart murmur clinic, echocardiography.

Correspondence
James Pemberton, Department of Cardiology, Dunedin Hospital, Private Bag 1921, Dunedin 9054, New Zealand.
Email: james.pemberton@southerndhb.govt.nz

Received 24 May 2016; accepted 7 November 2016.

doi:10.1111/imj.13331

Abstract

Background: Auckland City Hospital (ACH) established a Heart Murmur Clinic (HMC) with the aim of providing prompt assessment of patients with asymptomatic systolic murmurs. This may lead to early intervention and improved outcomes if significant structural heart disease is detected and reassurance if no significant findings are found. Similar clinics for children have proven beneficial; the benefit of a HMC in an adult population has been difficult to determine.
Aim: To review the clinical demographics and echocardiographic information of patients presenting to our HMC, to assess what proportion of significance structural heart disease had and determine the common structural abnormalities in this population.
Methods: This is a retrospective review of patients aged ≥15 years presenting to our HMC between March 2010 and December 2015 with an asymptomatic systolic murmur. Patients with previous cardiac surgery or known congenital or valvular heart disease were excluded.
Results: A total of 1221 patients was reviewed over the 5-year period; 980 underwent echocardiography. Significant cardiac disease was detected in 156 patients, with 23 patients requiring surgical intervention over the 5-year period. Significant aortic stenosis ($n = 43$) and mitral regurgitation ($n = 48$) were the most common pathologies. Patients > 65 years were more likely to have structural heart disease (16% vs 11%, $P < 0.05$).
Conclusion: Establishing a HMC has allowed the screening of a large number of patients who would otherwise have low priority for assessment. We have identified a large proportion with significant structural disease, which has allowed for early surgical intervention when appropriate and may potentially result in improved patient outcomes.

Funding: None.
Conflict of interest: None.